Schering-Plough

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004D-0117; International Conference on Harmonisation; Draft Guidance on E2E Pharmacovigilance Planning

Dear Sir/Madam:

Schering-Plough has reviewed the Draft Guidance for Industry on E2E Pharmacovigilance Planning, and we offer the following comments for your consideration.

1. In the Annex-Pharmacovigilance Methods, section 1. Passive Surveillance, under "*Systematic methods for Evaluation of spontaneous reports,*" it is implied that data mining methodologies can ascertain risk, "Caution should be exercised if using this tool for evaluating the magnitude of risk or for comparing safety risks between drugs." These methodologies merely show whether or not a drug-event combination occurs disproportionally more than expected based on statistical models, which does not necessarily imply risk.

2. This comment refers to the Annex section 3. Active Surveillance, Registries. Specifically, the sentence "A disease registry might also be used as a base for a case-control study comparing the drug exposure of cases identified from the registry and controls selected from either patients within the registry with another condition, or outside the registry." Doing this might result in information bias, which is potentially introduced when the exposure information gathering methodology differs between cases and controls.

The following comments refer to the Annex section 4. Comparative Observational Studies.

3. Under Cross-sectional study (survey), there is a sentence "These studies can also be used to examine the crude association between exposure and outcome in ecologic analyses." Because of the "ecologic fallacy", these analyses are only useful to generate hypotheses.

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4. Under Case Control Study, there is a sentence "The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease in the two groups." The odds ratio is merely a reasonable approximation of the relative risk, provided that the cumulative incidences during the risk period are low; i.e., less than about 20 percent, and that the prevalence of the exposure remains reasonably constant during the study period.

Schering-Plough appreciates the opportunity to comment on this guidance document.

Sincerely,

Gretchen Trout
Director, Regulatory Affairs and Policy
Global Regulatory Affairs